REMARKS

Reconsideration of the application in view of the above amendments and following remarks is respectfully requested.

Claims 1-3 and 5-10 were pending in the subject application. As recited above, claims 2, 3, 6, 7 and 10 have been amended. Claims 2 and 3 have been amended for purposes of clarity to insert the full names for the abbreviations contained therein. Support for the language is found, for example, at page 6, lines 26-27, and page 7, line 5, of the subject application. Claims 6 and 10 have been amended to enhance the clarity. Support for the language is found, for example, at page 7, lines 13-17, of the subject application. Claim 7 has been amended to enhance the clarity. Support for the language is found, for example, in claim 1 as filed and at page 6, lines 4-6, of the subject application. New dependent claims 11-14 have been added to more thoroughly set forth the claimed invention. Support for the new claims is found, for example, at page 3, lines 23-25; page 6, lines 1-3; and page 10, lines 18-20, of the subject application. No new matter has been added by the amendments and new claims. Therefore, claims 1-3 and 5-10 as amended above, and new claims 11-14 are now pending in the subject application.

In the Office Action dated November 19, 2002, claims 2 and 3 which depend from claim 1 were objected to for the informality of containing the abbreviations "HPLC" and "DHPLC", respectively.

As set forth above, claims 2 and 3 have been amended to insert the full name of each abbreviation. Therefore, it is believed that this objection has been obviated.

Reconsideration and withdrawal of this informality objection are respectfully requested.

In the Office Action, claims 6, 7 and 10 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. This rejection is respectfully traversed.

Applicants respectfully disagree that claims 6 and 10 as originally filed were indefinite for the recitation of the term "larger". This term as recited in original claims 6 and 10 was within the phrase "wherein the DNA comprises one or more fragments of a larger DNA molecule". This simply said that the DNA was one or more fragments of a DNA molecule. A

DNA fragment of a DNA molecule must necessarily be smaller than the DNA molecule. Therefore, the DNA molecule must be larger than one or more of its fragments.

Nevertheless, in order to expedite prosecution, claims 6 and 10 have been amended to replace "larger DNA molecule" with "gene". Therefore, Applicants believe that this grounds of rejection under Section 112, second paragraph, has been overcome.

Claim 7 was rejected under Section 112, second paragraph, as indefinite on the grounds that there is insufficient antecedent basis for the term "side product". As set forth above, claim 7 has been amended to replace "side product" with "synthetic failures" which is recited in claim 1 as originally filed. Therefore, Applicants believe that this grounds of rejection under Section 112, second paragraph, has been overcome.

Therefore, Applicants believe that the rejection of claims 6, 7 and 10 under 35 U.S.C. § 112, second paragraph, has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

In the Office Action, claims 1, 3, 5, 6 and 8-10 were rejected under 35 U.S.C. § 103(a) as unpatentable over Huber et al. (Anal. Chem. 68:2959-2965, 1996) in view of Tang et al. (U.S. Patent No. 5,668,268) and Agabian et al. (U.S. Patent No. 5,770,714). This rejection is respectfully, but strenuously, traversed.

Applicants disagree that Huber et al., Tang et al. and Agabian et al., taken alone or in combination, render any of the pending claims unpatentable under 35 U.S.C. § 103(a). There is no teaching or suggestion in any of the cited references that would have provided motivation to one of ordinary skill in the art at the time of the subject invention to combine the cited references. Furthermore, even if it was legally permissible to combine the cited references, the combination nevertheless still fails to provide Applicants' claimed invention. It is respectfully submitted that the Patent Office has failed to establish a *prima facie* case for obviousness under Section 103(a).

The Office Action has not provided the requisite evidence of motivation (to combine the cited references) that meets the legal requirements under Section 103(a) for sufficiency to combine the references. There is no citation in the Office Action to where in Huber at al., Tang et al. or Agabian et al., there is a teaching or suggestion to combine the references to attempt to meet all the elements of the invention as claimed.

The Office Action does cite to the M.P.E.P. at 2144.07 and 2144.09 as allegedly providing support for the motivation for combining the cited references for the obviousness rejection. Applicants respectfully disagree.

In the preparation of synthetic double-stranded oligonucleotides, the initial fragment population is greater than 99% identical in DNA sequence, length and base composition, and will appear as a single band on standard agarose or acrylamide gels and as a single peak in standard high performance liquid chromatography (HPLC). The disclosure of the present invention shows surprisingly that this population of synthetic double-stranded oligonucleotides which appears homogenous to most analytical methods can be separated into two populations, and that this separation has the useful property of allowing the isolation of a population of synthetic double-stranded oligonucleotides which is depleted of synthetic failures. This population permits the preparation of larger synthetic double-stranded oligonucleotides, such as synthetic genes, that have improved sequence fidelity.

In contrast, Huber et al. describes a method for detecting and characterizing DNA fragments (from digested cloned DNA) that contain A:T-rich regions. Specifically, Huber et al. shows that the effect of temperature on DNA fragment mobility is much stronger for fragments with A:T-rich regions than for fragments with a more uniform base composition. At higher temperatures, the fragments no longer elute in order of length, rather, fragments with A:T-rich regions can elute sooner than shorter fragments without A:T-rich regions. Thus in Huber et al., there is no teaching or suggestion that fragments containing synthetic failures will show regional melting, and no teaching or suggestion that such fragments would show altered mobility.

Furthermore, in Huber et al., all the fragments that elute in a single peak are homogenous (i.e., every molecule within a particular peak is the same). In addition, in Huber et al., there is very low sequence similarity between fragments of different lengths, and no two fragments of the same length. Thus in Huber et al., there is no teaching or suggestion that highly similar fragments can be separated by ion-pair reversed-phase chromatography, and no teaching or suggestion that this separation will have the beneficial effect of removing synthetic failures from the population.

Tang et al. describes passivated organic polymer supports, processes for their preparation and processes for their use in oligonucleotide synthesis that allow for highly efficient solid phase synthesis of oligonucleotides. Tang et al. teaches that for whatever problems exist with the use of controlled-pore glass (CPG) in oligonucleotide synthesis, one of ordinary skill in the art need look no further than their invention. There is no teaching or suggestion in Tang et al. of the effect of synthetic failures on hybridization or melting point. Furthermore, there is no teaching or suggestion in Tang et al. that physical properties that manifest in duplex oligonucleotides would facilitate the separation of synthetic failures for accurate sequences.

It is well settled law that, in order to combine the teachings of prior art to establish obviousness under 35 U.S.C. § 103, there must be some teaching or suggestion that the combination be made. There is no teaching or suggestion in Huber et al., Tang et al. or Agabian et al. that the references should be combined. The Office Action further cites to the M.P.E.P. at 2144.07 and 2144.09 as providing justification for the motivation to combine the cited references and make the substitution for the elements of Applicants' claimed invention not provided by the cited references. These two M.P.E.P. sections, like the cited references themselves, do not provide justification for motivation to combine the cited references. (The latter part regarding substitution of elements is addressed below.) Therefore, Applicants respectfully disagree that the combination of Huber et al., Tang et al. and Agabian et al. is proper under Section 103(a).

Even assuming for the sake of argument that the combination of Huber et al., Tang et al. and Agabian et al. was legally proper, the combination fails to yield the claimed invention. Tang et al. and Agabian et al. do not teach the methodology employed in Applicants' claimed invention. The teachings of Huber et al. are clearly insufficient to remedy the deficiencies of Tang et al. and Agabian et al. relative to the subject methods as claimed. For example, the Office Action attempts to justify a replacement of the DNA restriction fragments from digestions of plasmids in Huber et al., with the synthetic double-stranded oligonucleotides of Applicants' claimed methods by citing to the M.P.E.P. at 2144.07 and 2144.09. Firstly, it is not obvious to substitute the DNA restriction fragments of Huber et al. which are of varying lengths and are not highly similar in nucleic acid sequence, with Applicants' synthetic double-stranded oligonucleotides which are nearly identical in length, base composition and sequence. The DNA restriction fragments of Huber et al. and the synthetic double-stranded

oligonucleotides of the present claimed invention do not have the close structural similarity required in the cases cited in the M.P.E.P. at 2144.09. Accordingly, the M.P.E.P. at 2144.09 is not applicable. Secondly, as discussed in detail above, the intended purpose of the methods taught in Huber et al. (e.g., see "CONCLUSIONS" at page 2965) is for the detection of partial denaturization in A:T-rich DNA fragments by ion-pair reversed-phase chromatography. Based on Huber et al., one of ordinary skill in the art would only select double-stranded oligonucleotides which are A:T-rich. This is not Applicants' claimed invention; there is no such requirement in Applicants' claimed methods that the synthetic double-stranded oligonucleotides are A:T-rich. Therefore, it would have been necessary to modify the A:T-rich DNA fragments of Huber et al. in a nonobvious manner in order to yield the synthetic double-stranded oligonucleotides of Applicants' claimed invention. Accordingly, the M.P.E.P. at 2144.07 is not applicable.

Even assuming that the combination of Huber et al. Tang et al. and Agabian et al. was legally proper and further that the motivation to modify the method of Huber et al. existed, there was no reasonable expectation that synthetic double-stranded oligonucleotides that are nearly identical in length, base composition and sequence could be successfully separated. As described in Huber et al. and discussed above, the separation in Huber et al. is based upon the presence of A:T-rich regions which are not required in Applicants' claimed methods. Thus, Huber et al., Tang et al. and Agabian et al., taken alone or in combination, provided no reasonable expectation that one could have successfully separated synthetic double-stranded oligonucleotides that are nearly identical, through the use of the method of Huber et al. Accordingly, Huber et al., Tang et al. and Agabian et al., taken alone or in combination, did not provide to one of ordinary skill in the art at the time of Applicants' invention a reasonable expectation of success for Applicants' claimed methods.

Applicants respectfully, but strenuously, submit that the Patent Office has not met its burden of establishing a *prima facie* case for obviousness of the claimed invention.

Therefore, Applicants believe that the rejection of claims 1, 3, 5, 6 and 8-10 under 35 U.S.C. § 103(a) has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

New dependent claims 11-14 also distinguish patentably over the cited references, taken alone or in combination.

Therefore, in light of the amendments and remarks set forth above, Applicants believe all the Examiner's rejections have been overcome. Reconsideration and allowance of the pending claims (1-3 and 5-14) are respectfully requested. If there is any further matter requiring attention prior to allowance of the subject application, the Examiner is respectfully requested to contact the undersigned attorney (at 206-622-4900) to resolve the matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

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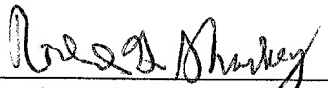
PATENT TRADEMARK OFFICE

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



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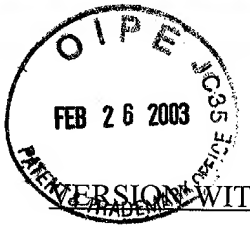

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2, 3, 6, 7 and 10 have been amended.

Claims 11-14 have been added.

2. (Amended) A method according to claim 1, wherein the column chromatography is high performance liquid chromatography (HPLC).

3. (Amended) A method according to claim 1, wherein the column chromatography is denaturing high performance liquid chromatography (DHPLC).

6. (Amended) A method according to claim 5, wherein the DNA comprises one or more fragments of a ~~larger DNA molecule~~gene.

7. (Twice Amended) A method according to any one of claims 1-3, wherein the ~~side product~~ synthetic failures separated ~~is a~~ are ~~molecule~~ molecules containing a uridine, apurinic, apyrimidinic or diaminopurine residue.

10. (Amended) A method according to claim 9, wherein the DNA comprises one or more fragments of a ~~larger DNA molecule~~gene.

11. (New) A method according to claim 5, further comprising joining oligonucleotides from the population depleted of synthetic failures, to other synthetic oligonucleotides.

12. (New) A method according to claim 11, wherein a gene or gene fragment is formed when the oligonucleotides are joined.

13. (New) A method according to claim 9, further comprising joining oligonucleotides from the population depleted of synthetic failures, to other synthetic oligonucleotides.

14. (New) A method according to claim 13, wherein a gene or gene fragment is formed when the oligonucleotides are joined.

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